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# Development of methods for studying the physiology behind the recovery of individuals after stroke

– PhD THESIS –

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A journey is ending, a new one is starting.

March 2011

Simona D.I. Nielsen

<b>MOTIVATION FOR THIS RESEARCH.....</b>	<b>7</b>
REFERENCES .....	10
<b>CHAPTER 1 .....</b>	<b>12</b>
<b>INTRODUCTION.....</b>	<b>12</b>
1.1 CORTICAL PLASTICITY .....	13
1.2 MOTOR LEARNING: IMPLICATIONS FOR REHABILITATION .....	14
1.3 THERAPIES.....	17
1.4 NEURONAL CHANGES THAT FOLLOW THE THERAPIES .....	23
1.5 PhD PROJECT GOALS .....	26
1.6. ORGANIZATION OF PhD THESIS.....	30
REFERENCES .....	32
<b>CHAPTER 2 .....</b>	<b>38</b>
<b>METHODOLOGY .....</b>	<b>38</b>
2.1 TECHNIQUES TO STUDY CORTICAL REORGANIZATION .....	38
2.2 ACTIVITIES STUDIED WITH THE COMPLEXITY OF DISTINGUISHING.....	39
2.3 STUDYING LEARNING .....	44
REFERENCES .....	46
<b>CHAPTER 6 .....</b>	<b>47</b>
<b>DISCUSSIONS .....</b>	<b>47</b>
6. 1 STUDY 1 .....	47
6. 2 STUDY 2 .....	49
6.3 STUDY 3 .....	50
REFERENCES .....	54
<b>CHAPTER 7 .....</b>	<b>55</b>
<b>CONSIDERATIONS AND FUTURE PROSPECTIVES .....</b>	<b>55</b>
REFERENCES .....	57
<b>SUMMARY .....</b>	<b>58</b>
<b>SAMMENFATNING .....</b>	<b>61</b>

## List of abbreviations

ARAT	Action Research Arm Test
BOLD	blood oxygen-level dependent
CIMT	Constraint Induced Movement Therapy
CNS	Central Nervous System
EEG	Electroencephalography
ERP	Evoked responses potentials
ES	Electrical stimulation
fMRI	functional Magnetic Resonance Imaging
FES	Functional Electrical Stimulation
FET	Functional Electrical Therapy
MEG	Magnetoencephalography
MRCPs	Movement related cortical potentials
PET	Positron Emission Tomography
SII	Secondary somatosensory areas
tFES	therapeutic FES
TENS	Transcutaneous electrical nerve stimulation
TMS	Transcranial magnetic stimulation
VR	Virtual Reality

## MOTIVATION FOR THIS RESEARCH

### Rationale for neuroimaging research: understanding the mechanism

Motor impairment after stroke is common following damage to areas of the brain normally involved in planning and executing motor commands. Regeneration of damaged tissue in adults is limited, which suggests that real improvement in motor function observed over weeks or months following stroke is a consequence of reorganization of the surviving elements of the motor network. The mainstay of treatment is neurorehabilitation (Popović et al. 2003; (Rossini et al. 2003; Popović et al. 2004; Young and Forster 2007). The overall approach is effective and the benefit of strategies aimed at helping patients adapt to impairment well proven (Ward et al. 2003). A better understanding of the mechanisms underlying recovery (or deterioration) of function after a CNS lesion, as well as those leading to maladaptive or unfavourable outcomes, would be essential for directing specific and effective rehabilitative strategies as well as avoiding potentially harmful interventions (Rossini et al. 2003).

The biological basis of post-stroke recovery of function, particularly that occurring after following a rehabilitation therapy, has long remained elusive. In spite of clinical research (Ward et al. 2003; Weiller et al. 1992; Cramer et al. 1997; Marshall et al. 2000), there is a lack of objective methodologies applicable to humans. The decision regarding the choice of the appropriate therapy to patient subgroups is based on clinical examination and specialists' experience. It should take in account the best fit between the neural status of the patient and the expected neural consequences of the therapy.

The success of a treatment depends on the ability to drive functionally relevant reorganization in surviving brain regions and networks. This will vary dramatically across patients. Neuroimaging techniques can allow the assessment of how treatments interact with residual functional anatomy, which will inform mechanisms of action and allow targeted application of therapies based on neuroscientific principles (Ward 2005).

Functional Electrical Stimulation (FES) is used in the rehabilitation therapy of patients after stroke to improve their motor abilities. Its principle lies in applying repeated electrical stimulation to the relevant nerves or muscles for eliciting either isometric or concentric contractions of the treated muscles (Blickenstorfer et al. 2009).

Electrical stimulation (ES), when paired with voluntary component (therapeutic FES), appears to facilitate recovery in an additive or interactive way, in clinical studies (Popović et al. 2003; Popović et al. 2004; Popović et al. 2002). Enhancing plasticity is creating a permissive state for learning. Results from studies where therapeutic FES was applied in acute and in chronic hemiplegia, suggest better recovery of function compared with conventional treatment (Popović et al. 2004).



An open issue is represented by the mechanisms for these observed effects. Electrical stimulation is proposed to work through a sensorimotor coupling mechanism (Cauraugh et al. 2000; Woldag and Hummelsheim 2002). Increased proprioceptive signals from evoked movements are thought to bombard the somatosensory cortex (Cauraugh et al. 2000; Rosenkranz and Rothwell 2006), thereby increasing motor corticoneuronal excitability (Ridding and Taylor 2001; Luft et al. 2002; Sawaki et al. 2006). The increased motor cortical excitability may, then, facilitate greater voluntary activation of the relevant neuronal network that, again, lead to improved function (Wu et al. 2005).

Applying electrical stimulation with voluntary movement (tFES) provides an intensive traffic of neural information towards the brain, which occurs in a predictable manner, and that this may promote neural plasticity (Popović et al. 2003). Kinematic studies (Popović et al. 2003; Popović et al. 2004) demonstrated spatial and temporal reorganization of the movement and a novel coordination between neighboring joints as measured by the Drawing test (Eder et al. 2005). This suggests that its effect is not only peripheral, but that it, somehow, facilitates cortical changes.

While the positive benefits of therapeutic FES intervention following stroke are readily apparent, no investigation to date has examined the specific mechanism that may contribute to optimal motor output in the hemiplegic hand. Several reports have demonstrated that motor training causes cortical reorganization and somatosensory inputs lead to changes in the cortical excitability (Ridding and Taylor 2001; Kaelin-Lang et al. 2005). Therapeutic FES uses both somatosensory inputs and passive movements as means to improve motor performances (Lotze et al. 2003).

Neuroimaging studies demonstrated that passive movements result in cortical reorganization, meaning mere external treatment caused changes in functional brain activations to resemble the ones elicited by active movements (Lotze et al. 2003; Weiller et al. 1996; Carel et al. 2000). However, Lotze et al 2003 and a recent study from Kaelin-Lang et al. 2005 found that active training leads to better motor performance and more prominent increases in fMRI activation than passive training. Their findings consolidate the pivotal role of voluntary drive in motor learning and neurorehabilitation.

However, the functional brain correlates of therapeutic FES have yet to be determined. Having a good understanding of how therapeutical FES may interact with the central nervous system may therefore be crucial to improve and optimize the treatment. Noninvasive techniques to study brain function, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), could help to document the relationship between cortical reorganization and the recovery of motor function (Rossini et al. 2003). It is possible that the clinical results reported with therapeutic FES are due to the enhanced cortical plasticity from the cumulative effects of increased cortical excitability due to FES with those due to voluntary activation. The lack of this knowledge was the motivation for this project. The purpose of this

research was to contribute to the understanding of the neural consequences of the applied therapeutic FES to promote reaching and grasping and this was materialized in Study 1 and Study 2.

In addition, plasticity of the cortex is considered as learning of novel tasks. The necessity for learning comes after stroke due to the fact that proprioception/exteroception is modified and motor pathways do not operate; however the vision works fine. Scientists now are trying to determine how exactly practice makes perfect, how the brain learns the physical properties of its own body, and how the visual system coordinates with the motor system (Krakauer 2006). As Krakauer describes, simply reaching out one's hand involves translating a vast series of physical and visual properties into action: Extrinsic, vectorial coordinates seen in the visuomotor system must be transformed first into proprioceptive coordinates and then into intrinsic muscle coordinates.

In parallel with the neural consequences of the therapeutic FES, we were interested in other aspects such learning of a novel task. This led us to Study 3 where we are presenting how the learning takes place when vision is modified, while the proprioception/exteroception and motor pathways are intact.

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# CHAPTER 1

## INTRODUCTION

In this chapter, we provide background information, introduce terms used throughout the thesis, set the aim of the thesis, define open problems, and formulate research questions that are to be answered by the thesis. Overall goal of this research was to develop a set of objective methods and tools that can study plasticity induced by different experimental conditions. The methods that we propose here should be understood as contribution to the actual effort of the researchers in the rehabilitation field. This tool should distinguish between the experimental conditions and should find application later in the rehabilitation field. Specifically, the aim was to develop a tool for study plasticity induced by therapeutic FES. In parallel with the neural consequences of the therapeutic FES, the learning process that takes place when vision is modified while the proprioception/exteroception and motor pathways are intact was investigated.

Stroke is a major cause of impairment and functional disability in millions of people worldwide (Rossini et al. 2003; Young and Forster 2007). A stroke can be seen as a massive distortion of the capacity of the brain to process neural information, with heterogeneous consequences. The residual impairment in a number of functions fundamental for everyday activities, such as movement programming and execution, sensorimotor integration, language, and other cognitive functions have a chronic impact on overall level of functioning and quality of life. Not only the motor system is affected after a stroke, but also the cognitive and emotional systems may be seriously impaired (de Vries and Mulder 2007).

It is estimated that after acute stroke approximately 80% of the patients have some form of motor impairment (Barker and Mullooly 1997). About 20% of these patients regain at least part of their lost motor functions in the subsequent months; thus, of the patients surviving stroke, 50–60% are left with a chronic motor disorder (Hendricks et al. 2002). These disorders are often related to balance, timing and co-ordination, and to loss of strength and/or spasticity in the affected limbs.

Although stroke damage can be devastating, many patients survive the initial event and undergo some spontaneous recovery, which can be further augmented by rehabilitative therapy (Murphy and Corbett 2009). Hesse suggests that the goal of rehabilitation is to enable an individual who has experienced a stroke to reach the highest possible level of independence and be as productive as possible (Hesse et al. 2005).

Rehabilitation aims to enable stroke patients to regain hand/arm/leg function, as well as other vital functions, and to return to independent life-style in the easiest, simplest, and fastest way. Efficacy of rehabilitation depends on the degree of initial severity of stroke and the initial treatment, as well as on the

time interval from stroke to initiation of voluntary movement. Rehabilitation encompasses various techniques which are used to manipulate elements of the central and peripheral nervous system and includes traditional conventional motor therapy, constraint intensive movement therapy, amphetamine, mirror therapy, and electrical stimulation (Ward and Cohen 2004a; Homberg 2005; Ward 2005b; Krakauer 2006).

It is clear from clinical studies that post-injury training is an important element in promoting recovery. The quality of the post-injury experience is crucial to the rate and extent of recovery. Much therapeutic effort is invested in functional recovery of motor skills after stroke (de Vries and Mulder 2007).

## **1.1 CORTICAL PLASTICITY**

For many years, the central nervous system (CNS) has been viewed as a rigid structure with little capacity for modification and adaptation. In the last two decades, however, there has been a paradigm shift characterized by the understanding of the CNS as a plastic organ, capable of adaptation or modification when confronted with environmental challenges or lesions (Celnik and Cohen 2004a).

In this chapter, we are discussing strategies geared to influence motor function and cortical plasticity in the human CNS.

Santiago Ramon Y Cahal stated that the production of new neurons occurs only in the developmental stages of life and never in the adult organisms.

*But the functional specialization of the brain imposed on the neurones two great lacunae; proliferative inability and irreversibility of intraprotoplasmic differentiation. It is for this reason that, once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.*

–Santiago Ramon y Cajal

More than 50 years ago, Donald Hebb postulated that increments in synaptic efficacy occur during learning when firing of one neuron repeatedly produces firing in another neuron to which it is connected, leading to the notion of plasticity as a behavioral adaptation (ie, learning) that is associated with a change of function at the level of the synapse.

Details of cortical map structure are largely created and altered by experience. If a body part becomes less or more active, such as by deafferentation or by repeated use in learning paradigms, its topographical representation in the somatosensory cortex shrinks or enlarges, respectively (Merzenich et al. 1983; Recanzone et al. 1992; Buonomano and Merzenich 1998). Often, these changes cause proportional

enlargement or shrinkage of adjacent cortical representational areas, apparently in order to utilize cortical space and neurons more efficiently.

Experiments in both animals and humans show that some regions in the normal adult brain, particularly the cortex, have the capacity to change structure and consequently function during learning or in response to exposure to enriched environments. This process is often referred to as plasticity (Ward 2005a). Neuroplasticity occurs in the brain 1) at the beginning of life: when the immature brain organizes itself, 2) in case of brain injury: to compensate for lost functions or maximize remaining functions, 3) through adulthood: whenever something new is learned and memorized.

The brain has a remarkable ability to reorganize its neural connections in response to sensory stimulation and after injury. It is believed that the adaptations in the brain in response to injury (i.e. plasticity) are correlated with recovery of function and are effected by rehabilitation therapies (Ward 2005b). Brain plasticity is why intensive therapy is such a critical element of stroke recovery (Rossini et al. 2003; Ward and Cohen 2004b). The best rehabilitation strategies, therefore, will enhance cortical plasticity.

Two related factors enable plasticity in the adult brain after stroke. First, a surprising amount of diffuse and redundant connectivity exists in the CNS and, second, new structural and functional circuits can form through remapping between related cortical regions (Murphy and Corbett 2009).

Functional recovery is attributed to reorganization processes in the damaged brain. Within-system reorganization (selforganization) may be possible when damage to a functional system is partial. However, when a functional system is completely damaged, recovery is achieved largely by a process of substitution, i.e. other brain areas are recruited to take over the functions of the areas damaged by stroke (de Vries and Mulder 2007; Seitz and Freund 1997).

The efficiency and speed of the (motor) recovery process depends partly on the availability of (sensory) information provided by motor activity (Kwakkel et al. 2004). Traditionally, 5 sources of information can be distinguished in relation to motor relearning: (1) proprioceptive information; (2) tactile information; (3) vestibular information; (4) visual information; and (5) (to a lesser extent) auditory information (de Vries and Mulder 2007).

## **1.2 MOTOR LEARNING: IMPLICATIONS FOR REHABILITATION**

Rehabilitation, for patients, is fundamentally a process of relearning how to move to carry out their needs successfully (Gilmore and Spaulding 2001). Motor learning theories have contributed to the way rehabilitation therapists work with people who have experienced a CVA and motor learning principles have been applied to the functional retraining of clients with neurological impairments (Krakauer 2006). There are four factors that contribute to motor learning: stages of learning, types of task, practice, and

feedback. All four factors must be considered by clinicians when designing treatment programs for patients who have experienced a CVA. Practice and feedback are considered to be the two most important factors in skill acquisition (Krakauer 2006).

(Xu et al. 2010) did an experiment with one month old mice. They taught the mice a task and then imaged their brains, at the level of individual dendrites. They showed that, within one hour of the training session, the mice that did well at the task (that is, had learnt it to some extent), had an increase in dendritic spines of about 10%. That is, the brain had undergone structural as well as functional changes. What's more, about 50% of the new spines were still there two weeks later and, for mice training for 16 days, 40% of the new spines were still there three months later. The authors conclude: 'these data indicate that motor learning selectively stabilizes learning-induced new spines and destabilizes pre-existing spines. The prolonged persistence of learning-induced synapses provides a potential cellular mechanism for the consolidation of lasting, presumably permanent, motor memories.' 'Practice of novel, but not previously learned, tasks further promotes dendritic spine formation in adulthood' (Xu et al. 2010). Furthermore, they showed that different motor skills are encoded by different sets of synapses. Practice of novel, but not previously learned, tasks further promotes dendritic spine formation in adulthood. Their findings reveal that rapid, but long-lasting, synaptic reorganization is closely associated with motor learning. The study of how the brain rewires and regrows neurons after injury or to facilitate learning is one of the most exciting frontiers of neuroscience (Krakauer 2006).

Experiments in monkeys clearly demonstrate the importance of learning for recovery of function (Nudo and Friel 1999). A subtotal lesion confined to a small portion of the representation of one hand resulted in further loss of hand territory in the adjacent, undamaged cortex of adult squirrel monkeys if the hand was not used. Subsequent reaching relied on compensatory proximal movements of the elbow and shoulder. Forced retraining of skilled hand use, however, prevented loss of hand territory adjacent to the infarct. In some instances, the hand representations expanded into regions formerly occupied by representations of the elbow and shoulder. This functional reorganization in the undamaged motor cortex was accompanied by behavioral recovery of skilled hand function. These results suggest that, after local damage to the motor cortex, rehabilitative training can shape subsequent recovery-related reorganization in the adjacent intact cortex.

After focal brain damage work in animal models has clearly shown that the molecular and cellular substrates of plasticity are changed in both perilesional and distant brain regions (Schallert et al. 2000). There is also evidence of reduced GABAergic inhibition and increased hyperexcitability in both perilesional and distant cortex after focal injury. This finding is of particular interest as it is easier to induce long term potentiation, long considered a key substrate of learning, under such conditions



(Hagemann et al. 1998). Taken together, these changes suggest that the damaged brain is more amenable to activity driven changes in structure and consequently function. In other words it is more plastic. Similar injury induced changes are likely to occur in the human brain, and manipulation of these processes might provide a means of maximizing the recovery potential in patients with focal brain damage (Ward and Cohen 2004a).

***Prediction: forward model.*** The concept of forward internal model is a widely accepted tenant in motor control. The internal model hypothesis posits that there exist neural mechanisms that mimic the input/output characteristics of motor commands and compare this idealized output to actual performance signalled in the form of sensory feedback (Ito 1970; Ito 1970; Wolpert et al. 1995; Wolpert and Ghahramani 2000) (Ito 2005) . Internal models predict the sensory consequences of self-generated movements using efference copies of motor commands and they calculate feedforward motor commands from desired trajectory information. It believed that the construction of the internal model and its comparison with actual performance is carried out in the cerebellum (Ito 1970; Ito 2005; Blakemore et al. 1998; Blakemore et al. 2001). An accurate movement prediction then attenuates the sensation in the somatosensory cortex (Blakemore et al. 1998). These mechanisms are proposed to underlie motor adaptation/learning by using discrepancies between ideal and actual trajectories as sensory error signals to update internal model parameters in order to perform better the next time around.

The cerebellum is a likely site for a forward model of the motor apparatus that provides predictions of the sensory consequences of motor commands, which are then compared with the actual sensory feedback from the movement, according to computational and neurophysiological data. The error signals from this comparison may be used to modify motor commands during performance, to modulate neural responses to the sensory consequences of the movement, and to update the forward model (Blakemore et al. 2001).

The ability to predict the consequences of our own actions using an internal model of both the motor system and the external world has emerged as an important theoretical concept in motor control (Wolpert et al. 1995; Kawato et al. 1987; Jordan and Rumelhart 1992; Miall and Wolpert 1996). Such models are known as forward models because they capture the forward or causal relationship between actions, as signaled by efference copy and outcomes. Such forward models may play a fundamental role in coordinative behavior.

An experimental paradigm that is widely used to study motor learning involves having subjects hold the handle of a robotic arm and make planar reaching movements in a horizontal plane to visual targets displayed on a screen (Shadmehr and Mussa-Ivaldi 1994). When first exposed to the viscous curl field, subjects make skewed trajectories, but with practice are able to adapt to the force-field and again make

smooth and nearly straight movements. When subjects are in this adapted state and the force-field is turned off, ‘after-effects’ occur, with trajectories now skewed in the direction opposite to that seen during initial adaptation. The presence of after-effects is strong evidence that the central nervous system can alter motor commands to the arm to predict the effects of the force field and form a new mapping between limb state and muscle forces (internal model). Experiments indicate that internal models learned for one type of movement can generalize to other movements (Conditt et al. 1997). The importance of the concept of internal model to rehabilitation is that the model can be updated as the state of the limb changes. Thus rehabilitation needs to emphasize techniques that promote formation of appropriate internal models and not just repetition of movements (Krakauer 2006). They examined the effects of the removal of visual feedback during movement on the learning of both stable and unstable dynamics in comparison with the case when both vision and proprioception are available. Subjects were able to learn to make smooth movements in both types of novel dynamics after learning with or without visual feedback. By examining the endpoint stiffness and force after learning it could be shown that subjects adapted to both types of dynamics in the same way whether they were provided with visual feedback of their trajectory or not. The main effects of visual feedback were to increase the success rate of movements, slightly straighten the path, and significantly reduce variability near the end of the movement. These findings suggest that visual feedback of the hand during movement is not necessary for the adaptation to either stable or unstable novel dynamics. Instead vision appears to be used to fine-tune corrections of hand trajectory at the end of reaching movements.

### **1.3 THERAPIES**

Concepts from research in motor control can generate fresh thinking with regard to rehabilitation. There is a growing awareness that motor learning and motor recovery share overlapping neural substrates. Understanding the motor learning capability in stroke survivors has important practical implications for rehabilitation since the reacquisition of motor skills is an important part of functional motor recovery (Winstein et al. 1999). Ward and Cohen (Ward and Cohen 2004b) have suggested that it is important to maximize the neuronal input to the affected area. As an example, paretic hand recovery is improved by reducing the somatosensory input from the intact hand by cutaneous anesthesia or by the immobilization of the intact hand in patients undergoing constraint induced movement therapy (Taub and Uswatte 2003). Another strategy is to maximize the somatosensory input from the paretic hand with intensive exercise (Sunderland et al. 1992) or robot-induced therapy (Volpe et al. 2000) or to use repetitive low frequency transcranial magnetic stimulation directly on the somatosensory cortex (Peinemann et al. 2000; Schambra

et al. 2003). In this section we will review the rehabilitation techniques that to some extent rely on motor learning and relearning.

**Physical Therapy (PT).** For most stroke patients, physical therapy is the cornerstone of the rehabilitation process. A physical therapist uses training, exercises, and physical manipulation of the stroke patient's body with the intent of restoring movement, balance, and coordination. The aim of PT is to have the stroke patient relearn simple motor activities such as walking, sitting, standing, lying down, and the process of switching from one type of movement to another. Although exercise programs constitute an essential component of poststroke rehabilitation, stroke survivors may not regain enough voluntary motor control in the upper extremity with traditional rehabilitation methods to fully and effectively grasp and manipulate objects. To address this shortcoming, newer and more technologically advanced rehabilitation methods have been investigated (Young and Forster 2007).

**Constraint-Induced Movement Therapy (CIMT).** Traditional *physical therapy* has been criticized for its lack of intensity (Page 2003). Taub argued that one very important aspect in the rehabilitation process is the intensity with which the selected rehabilitation technique is applied to patients rather than its nature (Taub et al. 1993; Taub et al. 1999). Animal and human studies have shown that important variables in learning and relearning motor skills and in changing neural architecture are the quantity, duration and intensity of training sessions. There is evidence to demonstrate that plasticity is “use-dependent” and intensive massed and repeated practice may be necessary to modify neural organization (Taub et al. 1999). The decreased ability to use the affected limb is a common deficit in individuals who have had a stroke. The amount of movement performed with the affected limb is decreasing (learned non-use) and over time such a decrease in movement leads the brain to extinguish movements that are no longer being used. CIMT refers to a family of treatments for motor disability that combines constraint of movement, massed practice, and shaping of behaviour to improve the amount of use of the targeted limb (Taub et al. 1999). CIMT has two components and is usually given over 2 weeks: (i) restraint of the less-affected extremity for 90% of waking hours; (ii) massed practice with the affected limb for 6 hours a day using shaping (Krakauer 2006). CIMT has its roots in animal experiments. When the monkey's forelimbs were deafferented, the monkey ceased to use the affected limbs. This nonuse was ‘unlearned’ by restricting the intact limb with a sling. Restriction for 1 to 2 weeks resulted in restoration of use of the previously ignored limb (Taub and Uswatte 2003). This therapy has garnered a large amount of attention because it has shown that even patients with chronic stroke (> 6 months out) can show meaningful gains (Taub et al. 2003). Thus, there are many studies demonstrating that in human patients with an affected upper limb, a

positive therapeutic effect can be achieved following CIMT principles (Taub et al. 2003; Tarkka et al. 2005; Tarkka et al. 2008). One multicenter trial was also performed addressing the effects of CIMT in appropriate subjects within 3 to 9 months after stroke (Taub et al. 2006). Not surprisingly, the multicenter trial demonstrated that practice improved hand motor skills more than no practice.

### ***Electrical Stimulation.***

**Low TENS.** Low-TENS was first evaluated in 44 stroke patients. Three months of treatment resulted in a significant increase of motor function in the treatment group compared to controls; no decrease in pain or spasticity occurred (Sonde et al. 1998). The follow up of the use of Low-TENS after three years (Sonde et al. 2000) included 28 stroke patients. Fugl-Meyer Motor Assessment, Ashworth Scale to assess spasticity, and the Barthel Index scores showed that motor function of the paretic arm had deteriorated, and spasticity was increased in both groups.

**MESH Glove.** The glove is used with no intention to generate movement in three weeks, 20-minute sessions once or twice daily. Functional abilities were evaluated before and after MESH glove treatment (Modified Motor Assessment Scale, sensory and motor testing, somatosensory evoked potentials) in 51 chronic post-stroke patients (mean time 3.7 years post-onset of stroke). The results suggest improved arm and hand sensation, normalized hand temperature, decreased swelling, decreased spasticity, and improved voluntary motor control (Peurala et al. 2002).

**Cyclic Electrical Stimulation (ES).** Chae (Chae et al. 1998a; Chae and Yu 1999) suggested that active repetitive exercise induced by cyclic ES enhances motor recovery in sub-acute stroke. Stroke patients from the ES-treated group exhibited significantly greater upper extremity motor recovery than control subjects. However, the gains in motor function did not translate into significant improvement in the performance of basic self-care activities. Measures used to document the recovery were the Fugl-Meyer Motor Assessment and the Functional Independence Measure (FIM), conducted at the start and after 3 months of treatment.

Powell (Powell et al. 1999) studied 60 acute hemiparetic patients, 2 to 4 weeks after stroke. At both 8 and 32 weeks, the change in the isometric strength of wrist extensors was significantly greater in the ES group than in the control group. At week 8, grasp and grip subscores of the Action Research Arm Test (ARAT) increased significantly in the ES group compared with those in the control group.

**EMG-triggered electrical stimulation.** Francisco et al. (1998) assessed the efficacy of EMG triggered neuromuscular stimulation in enhancing upper extremity motor recovery and functional recovery of acute

stroke survivors. The subjects treated with EMG-triggered stimulation exhibited significantly greater gains in Fugl-Meyer and Functional Independence Measure (FIM) scores compared with controls. Cauraugh et al. (2000b) used electrical stimulation triggered by electromyographical (EMG) activity to improve hand function in poststroke subjects. The results indicated that participants in the treatment group achieved significantly higher gains on hand function tests and force generation measures following treatment when compared to a control group. EMG-triggered FES was also used by Chae et al. (2001) in an active repetitive movement training program for the finger extensors of stroke survivors in which notable improvements in function were obtained. Improvements in self-care tasks have also been observed following treatment with EMG-triggered FES as well (Francisco et al. 1998). A recent meta-analysis of EMG-triggered neuromuscular stimulation reveals that it is an effective post-stroke treatment in the acute, subacute and chronic phases of recovery (Krakauer 2006). Importantly, it has been shown that simple suprathreshold sensory stimulation, unrelated to movement, is of limited functional value (Krakauer 2006).

***Functional Electrical Stimulation (FES).*** In one of the earliest studies, Merletti et al. (1975) applied a 2 channel functional electrical stimulation in order to augment elbow and fingers/wrist extensions. The conclusions were that FES contributed greatly to recovery of hand and elbow movements in 5 stroke subjects, yet in the remaining 3, the improvement was significant only at the elbow joint.

Electrical therapy has been applied as a therapy in humans with central nervous system injuries although there are no definite conclusions on which technique works the best for a given indication. Kraft et al. (1992) reported that subjects assigned to electrical therapy improved their aggregated Fugl-Meyer score significantly from pretreatment to posttreatment, and the improvement was maintained at 3 and 9 month follow-ups. Feys et al. (1998) used FES for 6 weeks in stroke subjects. Subjects performed better on the Fugl-Meyer test compared to the control group throughout the study period, but differences were significant only at follow-up. Twenty-six subjects were randomly assigned to receive either neuromuscular stimulation or placebo (Chae et al. 1998b). The treatment group received surface neuromuscular stimulation to produce wrist and finger extension exercises and the controls received placebo stimulation over the paretic forearm 1 h per day for a total of 15 sessions. Parametric analyses revealed gains in Fugl-Meyer scores for the treatment group immediately and after 4 and 12 weeks of treatment. The Handmaster NMS-1 system is becoming widely used for therapy in stroke subjects (Nathan 1997). Evaluation of the Bionic Glove (Popovic et al. 1999), and the Belgrade Grasping System (Popovic et al. 1998) in chronic tetraplegic subjects showed that FES improves the reach and grasp. The common conclusions from all studies are that combined electrical stimulation and extensive physical

exercise with enhanced feedback contribute to the recovery and that the contribution is greater if the treatment is applied in a timely fashion, i.e., shortly after the stroke.

FES is used in the rehabilitation therapy of patients after stroke or spinal cord injury to improve their motor abilities. Its principle lies in applying repeated electrical stimulation to the relevant nerves or muscles for eliciting either isometric or concentric contractions of the treated muscles (Blickenstorfer et al. 2009). Electrical stimulation can be especially beneficial when traditional active-motor approaches may be difficult to implement (Gritsenko and Prochazka 2004).

**Functional Electrical Therapy (FET).** Most of clinical studies agree that active rehabilitation is better than passive and that early treatment leads to better recovery, as well as that task related exercise is important (Popović et al. 2002). Popović et al. (2002) found that electrical stimulation combined with a voluntary exercise program was more effective in improving hand function in stroke survivors when compared to a group not receiving electrical stimulation.

FET combines intensive voluntary activation of proximal muscles and patterned multichannel electrical stimulation of distal muscles providing grasp and release functions in the paretic hand (Popović et al. 2003; Popović et al. 2004). The essential difference between FET and other electrical stimulation methods is that while electrical stimulation assists the opening, closing, and releasing functions, in parallel, a hemiplegic subject can concentrate on manipulation, that is, on shoulder and elbow movements. This added ability to grasp and release objects motivates a hemiplegic subject to exercise in a functional manner, i.e., to practice typical movements that were part of his or her normal daily activities before the cerebrovascular accident (Popović et al. 2002; Popović et al. 2003).

**Direct brain stimulation.** Cortical stimulation can modify activity in the motor cortex in animals and modulates cortical plasticity in humans (Celnik and Cohen 2004b). For example, TMS synchronously applied to a human motor cortex engaged in a motor training task enhances use-dependent plasticity in the contralateral hand. These findings suggest that noninvasive cortical stimulation could represent an adjuvant to motor training in efforts to recover lost function after cortical lesions like stroke (Plautz et al. 2003).

Activity within the intact motor cortex may be down-regulated. In addition to local effects under the stimulated location, cortical stimulation applied to one site can induce distant effects on cortical function and behavior (Siebner et al. 2000). For example, TMS applied to one motor cortex elicits activation changes in positron emission tomographic scans in the opposite motor cortex (Ward and Cohen 2004b). Low-frequency repetitive TMS applied to one motor cortex down-regulates motor cortical excitability in

the homonymous motor representation in the opposite hemisphere (Schambra et al. 2003) consistent with the concept of a physiologic balance of reciprocal inhibitory projections between both hemispheres. Recent studies showed that this balance is disturbed in patients with cortical lesions such as stroke in the process of generation of a voluntary movement by the paretic hand. Specifically, some of these patients show an abnormally high interhemispheric inhibitory drive from M1 in the intact hemisphere to M1 in the affected hemisphere (Murase et al. 2004) a finding that is more prominent in more impaired individuals. Therefore, it is possible that one way to enhance motor function in the paretic hand is the down-regulation of activity in the ipsilateral, intact motor cortex (with the purpose of reducing abnormal inhibition from the intact to the affected hemisphere), a hypothesis under investigation. A previous study indeed showed that 1-Hz TMS applied to one motor cortex in healthy individuals results in improvements in motor performance in the ipsilateral hand (Kobayashi and Pascual-Leone 2003).

**Motor imagery.** Neural reorganization depends on the information provided by sensorimotor efferent-afferent feedback loops. It has, however, been shown that the motor system can also be activated "offline" by imagining (motor imagery) (de Vries and Mulder 2007). Motor imagery intervention also leads to an improvement in arm function compared to a control group in acute (Page 2001) and chronic (Liu et al. 2004) stroke patients. This suggests that motor imagery could potentially lead to recovery of basic motor skills.

**Virtual reality-based rehabilitation (VR).** The main idea behind VR is attractive and plausible, namely that it can provide a varied and enjoyable environment in which patients can sustain the motivation to practice for extended periods of time and attend to specific components of error feedback (Krakauer 2006). The critical questions that need to be answered before investing in expensive equipment concern whether motor learning in a virtual environment generalizes to the real world and whether there are advantages of practice in a virtual versus a real environment (Adamovich et al. 2009). There is affirmative evidence for both questions in patients with chronic stroke, trained on VR tasks for the hand and arm (Adamovich et al. 2009). Although these studies are small and have not included controls, they highlight the potential of an approach that emphasizes principles of motor learning and then amplifies them in the VR environment (Krakauer 2006).

**Interactive robotic therapy.** The use of robot-induced force-fields to study adaptation to dynamic perturbations and growing awareness that motor learning and motor recovery share overlapping neural substrates, led to the idea that robotic devices could be developed to provide rehabilitation. The first robot

rehabilitation trial used the robot to assist patients with an impedance controller when they made self-initiated planar reaching and drawing movements (Krebs et al. 1998). A study that compared robot assisted therapy with intensive conventional therapy showed a significantly greater benefit of the robot on both measures of impairment and activities of daily living. Robots can also be used to have patients adapt to novel force-fields, as has been done in healthy subjects. Studies (Volpe et al. 2000) are suggesting that patients with hemiparesis do not learn or implement new internal models as well as controls. Nevertheless, a force-field environment generated by the robot could challenge patients to learn an internal model in a varying environment. An advantage of the robot is that it provides a way to control and measure therapeutic efficacy of both robotic therapy and other rehabilitation techniques. Precise kinematic measurements can be obtained and, if patients are adequately constrained so that they cannot make compensatory trunk movements, it can be ascertained if true recovery, defined by the ability to make straight and smooth movements, can actually result from rehabilitation (Krakauer 2006).

#### **1.4 NEURONAL CHANGES THAT FOLLOW THE THERAPIES**

Plastic changes in the intact and lesioned CNS can be induced by a variety of experimental manipulations and daily life events (Ward and Cohen 2004b). Therapeutic strategies to promote recovery from stroke are now beginning to utilize current knowledge of neural plasticity and the neuromodulatory role of physical rehabilitation. Current interests are also focused on therapies that may enhance plasticity associated with recovery and rehabilitation

The key lesson from animal models of focal damage is that manipulation of environmental, behavioural, or pharmacological context does not have an effect on recovery on its own; rather it can influence the effect of a specific therapy. In other words some techniques seem to “condition” the brain, so that it is temporarily more responsive to afferent input, and the best chance of driving cerebral reorganisation and functional recovery occurs when the brain is most receptive to afferent signals (Ward 2005b). Reducing somatosensory input from the unaffected hand can lead to improvements in motor performance in the non-anaesthetised affected hand that briefly outlast the duration of the anaesthesia. Immobilising the unaffected hand to encourage use of the affected hand (constraint induced movement therapy) may also reduce somatosensory input from the unaffected hand. Increasing somatosensory input from the affected hand using median nerve stimulation has been shown to improve motor function in stroke patients. Increasing the excitability of affected hemisphere M1 by means of repetitive TMS as a means of “conditioning” the brain to be more responsive during therapy is an approach to the treatment of motor impairment (Ward 2005b).

This chapter discusses the influence of somatosensory input on motor function and cortical plasticity.



**CIMT.** fMRI and TMS methods have been used to analyze changes in brain activation after participation in CIMT (Tarkka et al. 2005; Tarkka et al. 2008; Kobayashi and Pascual-Leone 2003). This therapy leads to activation in the hemisphere ipsilateral to the affected limb and also to activation contralateral to the affected side in the undamaged hemisphere. Results of fMRI-studies suggest that gains in motor function produced by CIMT may be associated with a shift in laterality of motor cortical activation toward the undamaged hemisphere (Kobayashi and Pascual-Leone 2003). Another fMRI study observed new activation in the contralateral to the affected hand motor/premotor cortices in three subjects and increased activation of the ipsilateral to the affected hand motor cortex and SMA in two patients after CIMT (Hamzei et al. 2006). TMS data (Woldag et al. 2004; Ziemann 2004) point to a modulation in the excitability of the cortical hand motor area in the affected side after CIMT. These modulations, which can be excitatory and/or inhibitory, are reflections of cortical reorganization and the plastic changes occurring in response to the task-specific exercise. It seems that in order to obtain biological indications of reorganization, a definite learning component has to be present in the exercise regimen. The CIMT provides an increasingly difficult motor challenge with a motor learning component, and thus provides activation in the brain that may enhance reorganization related to motor control.

**Plasticity after FES.** Suggestions have been made that the benefits of FES may go beyond the peripheral muscular level and that cortical activity may be stimulated during this type of intervention as well. Short-term changes in motor-evoked potential and in cortical blood flow as an effect of peripheral ES were demonstrated with TMS (Barsi et al. 2008), positron emission tomography (Ledberg et al. 1995), magnetoencefalography (Lin and Forss 2002), and fMRI (Backes et al. 2000; Smith et al. 2003). Additionally, event-related synchronization was seen in electroencephalogram (EEG) measures during wrist movements induced by FES in healthy subjects, suggesting that the cortical processes that regulate active voluntary movement are similar to the cortical activity seen during FES (Houdayer et al. 2006). It is possible that the clinical results reported with therapeutic FES are due to the enhanced cortical plasticity from the cumulative effects of increased cortical excitability due to FES with those due to voluntary activation. Both ES and FES have been shown to lead to cortical reorganization (Blickenstorfer et al. 2009; Barsi et al. 2008). In addition, the repetition of even a simple movement can produce changes in cortical excitability that lead to a transient reorganization in motor connectivity (Classen et al. 1998). Moreover, active involvement in task performance leads to a substantial increase in cortical excitability compared to non-skilful or passive training and when combined with FES (Barsi et al. 2008).

Electrical stimulation is proposed to work through a sensorimotor coupling mechanism whereby increased proprioceptive signals from evoked movements activate the somatosensory cortex thereby increasing motor corticoneuronal excitability (Cauraugh et al. 2000a; Rosenkranz and Rothwell 2006). The increased motor cortical excitability may then facilitate greater voluntary activation of the relevant neuronal network thereby leading to improved function (Wu et al. 2005). It is possible that the additional proprioceptive and/or somatosensory information provided by the electrical stimulation is used in a forward internal model.

A good understanding of how therapeutic FES interacts with the central nervous system may allow us to improve the therapy. Noninvasive techniques to study brain function, including functional magnetic resonance imaging, could help to document the relationship between cortical reorganization and the recovery of motor function (Ward et al. 2003). (Blickenstorfer et al. 2009) demonstrated that fMRI experiments during FES are feasible and suggested that fMRI could be used to monitor cortical organization.

## **SUMMARY:**

Key point 1: Functionally relevant *reorganisation* occurs in the human brain after stroke.

Key point 2: Rehabilitation treatments aimed at *minimizing* impairment are a key part of the rehabilitation process.

Key point 3: Plastic changes in the CNS can be induced by *a variety of experimental manipulations* and daily life events. Each therapy will contribute in a way to recovery; *a therapy is better than no therapy*.

Key point 4: - *Two combined therapies works better* than one.

## **1.5 PhD PROJECT GOALS**

As presented in the previous sections there are some limitations regarding the choice of the appropriate therapy to post stroke patient. The decision should take in account the best fit between the neural status of the patient and the expected neural consequences of the therapy. In spite of clinical research, there is a lack of objective methodologies applicable to humans. Most researches would agree that any therapy the patient will follow, it will contribute to an extent to the functional recovery. However, the details of how the therapies operate to generate the recovery are still largely unknown.

The goal of this thesis was to develop a set of objective methods and tools that can study plasticity induced by different experimental conditions. The methods that we propose here should be understood as contribution to the actual effort of the researchers in the rehabilitation field. By analysing the state of the art in the rehabilitation field, we identified following open problems.

**PROBLEM 1:** Functional Electrical Stimulation is used in the rehabilitation therapy of patients after stroke to improve their motor abilities. Electrical stimulation when paired with voluntary component (therapeutic FES), appears to facilitate recovery in an additive or interactive way, in clinical studies. An open issue is represented by the mechanisms for these observed effects. Having a good understanding of how therapeutic FES may interact with the central nervous system may therefore be crucial to improve and optimize the treatment.

Electrical stimulation has been proposed to work via a sensorimotor coupling mechanism whereby increased proprioceptive signals from evoked movements activate the somatosensory cortex thereby increasing motor corticoneuronal excitability (Cauraugh et al. 2000; Luft et al. 2002; Ridding and Taylor 2001; Rosenkranz and Rothwell 2006; Sawaki et al. 2006; Woldag and Hummelsheim 2002). The increased motor cortical excitability may then facilitate greater voluntary activation of the relevant neuronal network, thereby leading to improved function (Wu et al. 2005). It is possible that the additional proprioceptive and/or somatosensory information provided by the electrical stimulation is used in a forward internal model.

Neuroimaging techniques could allow the assessment of how treatments interact with residual functional anatomy and allow targeted application of therapies. Noninvasive techniques to study brain function, including functional magnetic resonance imaging, electroencephalography, could help to document objectively the relationship between cortical reorganization and the recovery of motor function.

By analysing the problem, we formulated the following research questions:

**RESEARCH QUESTION 1:** Is fMRI an appropriate objective technique to evaluate the neural consequences of the therapeutic FES?

We started by applying fMRI technique to obtain objective information about the neural consequences of the therapeutic FES (Study 1). The study analysed the combining stimulation approaches with behavioural training (eg., motor, cognitive training) and its related neural network. The aim was to develop a tool for study plasticity induced by therapeutic FES. This tool should distinguish between the experimental conditions and should find application later in the rehabilitation field. The importance of studying the neural correlates associated with FES for clinical populations (ie., stroke) and therapeutic application constituted the motivation for conducting the research. The study subjects included were healthy individuals.

Additionally, the internal model concept is important in rehabilitation because the model can be updated as the state of the limb changes. Therefore rehabilitation may need to emphasize techniques that promote the formation of appropriate internal models rather than simple repetition of movements (Krakauer 2006). To determine if internal models are appropriately incorporated during FES-assisted voluntarily movement, one must test if internal model networks are appropriately engaged during the task.

**PROBLEM 2:** Functional MRI relies on the paramagnetic characteristics of deoxyhemoglobin, measuring its concentration changes in brain tissue, in response to task dependent neuronal activation. The fMRI technique gives a comprehensive view of the distributed network that governs a particular brain function and it allows a detailed analysis of the relationship between function and anatomy. EEG records electrical brain activity on a millisecond time scale and thus permits temporal dynamics of brain function to be analyzed. A more complete picture of the cortical reorganization and when and where changes take place could be obtained with multimodal approaches.

**RESEARCH QUESTION 2:** Is EEG an appropriate objective technique to evaluate the neural consequences of the therapeutic FES? Could EEG analysis complement our previous fMRI results helping through a better understanding of the mechanism by which therapeutic FES interacts with the central nervous system which may allow us to improve the therapy? More specifically: will different task-related afferent input be reflected in the modulation of alpha and beta rhythms and movement related cortical potentials?

**PROBLEM 3:** Plasticity of the cortex is considered as learning of novel tasks. The necessity for learning comes after stroke due to the fact that proprioception/exteroception is modified and motor

pathways do not operate; however the vision works fine. Scientists now are trying to determine how exactly practice makes perfect, how the brain learns the physical properties of its own body, and how the visual system coordinates with the motor system. By analyzing the problem, we formulated the corresponding research question:

**RESEARCH QUESTION 3:** how the learning takes place when vision is modified, while the proprioception/exteroception and motor pathways are intact?

Study 3 presents a novel tool to manipulate visual stimuli by virtually altering point of view and so visual feedback necessary to perform a visuoguided movement and to correct it online, in order to see the effect of that above the reaching/grasping performance and its kinematics parameters. This study is directly related to the results presented in the literature related to the so-called perceptual recalibration that takes place when the subject is exposed to the altered visual input. Namely, when there is a discrepancy between the seen and felt location of the object, the performance suffers. However, the sensory systems rapidly adapt to this discrepancy, returning perception and performance to near normal. One of the suggestions is that this adaptation consists of "recalibrating" the transformation between the visual and proprioceptive perception of spatial location because visuomotor adaptation is a perceptual recalibration that depends on the subject's familiarity with the trajectory.

The three performed studies are listed below together with their working hypotheses.

### **STUDY 1: Interaction of Voluntary Hand Movement and Electrical Stimulation in secondary somatosensory areas and the cerebellum during simulated therapeutic Functional Electrical Stimulation**

We designed an fMRI experiment to study brain activity evoked with three tasks hand grasp tasks involving voluntary motor activation (VOL), patterned electrical stimulation of finger flexor/extensor muscles to effect movement without voluntary activation (FES), and voluntary activation performed together with FES (FESVOL).

The internal model concept is important in rehabilitation because the model can be updated as the state of the limb changes. Therefore rehabilitation may need to emphasize techniques that promote the formation of appropriate internal models rather than simple repetition of movements (Krakauer 2006). To determine if internal models are appropriately incorporated during FES-assisted voluntarily movement, one must test if internal model networks are appropriately engaged during the task.

Based on the studies of (Blakemore et al. 1998b; Blakemore et al. 1999; Blakemore et al. 2001), which specifically test mechanisms of the internal model networks, we hypothesized that FESVOL, as opposed to FES would activate the motor part of the cerebellum (Grodd et al. 2001), in particular to make predictions of the sensory consequences of motor commands. In turn, this should reduce the SII activity in FESVOL compared with FES due to a better prediction of the sensory input.

Each subject was instrumented with surface stimulation electrodes positioned over the motor points of the finger flexors/extensors muscles on the right arm. A button press with the left index finger initiated patterned electrical stimuli (50 Hz, 200  $\mu$ s pulse duration, 8-15 mA pulse amplitude) to produce right hand opening and closing. Right index finger flexion/extension was recorded with a goniometer. FESVOL revealed greater cerebellar activity compared with FES alone and reduced activity bilaterally in secondary somatosensory areas (SII) compared with VOL alone. Reduced activity was also observed for FESVOL compared with FES alone in the angular gyrus, middle frontal gyrus and inferior frontal gyrus. These findings indicate that during the VOL condition the cerebellum predicts the sensory consequences of the movement and diminish the subsequent activation in SII. The decreased SII activity may reflect a better match between the internal model and the actual sensory feedback. The greater cerebellar activity coupled with reduced angular gyrus activity in FESVOL compared with FES may indicate that the cortex may interpret sensory information during the FES condition as an error-like signal due to the lack of a voluntary component in the movement.

## STUDY 2: The dynamics of cortical modulation associated with voluntary movement task and peripheral electrical stimulation task

The aim of this study was to investigate differences in the cortical activity evoked with three grasp tasks involving voluntary motor activation, patterned electrical stimulation of finger flexor/extensor muscles to effect movement without voluntary activation, and their combination. We assessed cortical function, using multichannel surface EEG, with analysis of alpha and beta oscillatory activity and movement-related cortical potentials (MRCPs). We hypothesized that the central processing of peripheral input would be reflected differently in the modulation of cortical alpha and beta oscillatory activity and MRCPs. The power spectra of EEG signal decreased in the alpha band bilaterally with movement initiation over the motor and parietal areas under FESVOL condition. Power also decreased in the beta band with an ipsilateral distribution over motor areas and a bilateral distribution over the parietal areas under the VOL condition, a contralateral distribution over motor areas under the FES condition and an ipsilateral distribution over the centro-parietal areas. In addition, the three tasks VOL, FES, and FESVOL

utilized a different distribution of brain areas for the preparation, execution and control phases of the movement as quantified by movement-related cortical potentials.

### STUDY 3: Learning of arm/hand coordination with an altered visual input

The focus of this study was to test a novel tool for studying motor coordination with an altered visual input. The altered visual input was created using special glasses that presented the view as recorded by a video camera placed at various positions around the subject. The camera was positioned at a frontal (F), lateral (L), or top (T) position with respect to the subject. We studied the differences between the hand trajectories while grasping between altered vision and normal vision (N) in ten subjects. The outcome measures from the analysis were the trajectory errors and the time of execution. We found substantial trajectory errors and an increased execution time at the beginning of the task. We also found that the trajectory errors decreased after three days of practice with the altered vision for 20 minutes per day, suggesting that recalibration of the visual systems occurred relatively quickly. The results indicate that this recalibration has occurred by movement training. The results also suggest that the recalibration is more difficult to achieve for altered vision in F and L conditions than in T condition.

## 1.6. ORGANIZATION OF PhD THESIS

The PhD thesis contains 7 chapters. The thesis starts with the motivation for this research. The main framework of the section was to consider the rationale and methods for conducting neuroimaging studies in the service of understanding mechanisms of recovery after therapeutic interventions.

**Chapter 1** provides background information, introduce terms used throughout the thesis, set the aim of the thesis, define open problems, and formulate research questions that are to be answered by the thesis.

**Chapter 2** presents the methods that were applied to answer the research questions. Chapters 3, 4 and 5 are based on the following articles:

**Chapter 3:** Simona Denisia Iftime Nielsen, Rune Jersin Vingborg, Thomas Sinkjær, Mark, Andreas Roepstorff & Michael James Grey. 'Interaction of electrical stimulation and voluntary hand movement in SII and the cerebellum during simulated therapeutic Functional Electrical Stimulation'. *Human Brain mapping journal* (DOI 10.1002/hbm.21191)

**Chapter 4:** Simona Denisia Iftime Nielsen, Thomas Sinkjær, Michael James Grey, Omar Feix do Nascimento. ‘The dynamics of cortical reorganization associated with voluntary and peripheral electrical stimulus’ (submitted)

**Chapter 5:** Simona Denisia Iftime Nielsen; Strahinja Došen, Mirjana Popović, Dejan Popović. ‘Learning of arm/hand coordination with an altered visual input’ (DOI pii: 520781)

**Chapter 6** summarizes how the applied methods answered the research questions.

**Chapter 7** includes considerations and future prospective.



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## **CHAPTER 2**

### **METHODOLOGY**

#### ***2.1 TECHNIQUES TO STUDY CORTICAL REORGANIZATION***

Research in humans is performed largely at the systems level using techniques such as functional magnetic resonance imaging, positron emission tomography, transcranial magnetic stimulation, electroencephalography, Magnetoencephalography. They all present both significant advantages and limitations (Rossini et al. 2003).

fMRI and PET permit measurement of measure regional blood flow and metabolic changes linked with function-related changes in neuronal firing level. These methods provide good anatomical resolution but relatively poor definition in the temporal domain. On the other hand, physiological techniques, such as EEG and MEG, have excellent temporal resolution (Williamson and Kaufman 1990; Ward and Cohen 2004; Houdayer et al. 2006). When combined, these tools provide the investigator with useful strategies to evaluate changes in brain organization associated with learning or lesions (Ward and Cohen 2004). TMS is a safe, non-invasive way to excite or inhibit the human cortex with high temporal resolution (Ward and Cohen 2004). TMS triggers transient electromyographic responses (motor evoked potentials) in the target muscles. Because TMS excites discrete brain regions, it can be used to map the motor cortex (Ward and Cohen 2004; Siebner et al. 2000; Schambra et al. 2003). EEG analyses the electromagnetic properties of neuronal activation (Rossini et al. 2003). MEG is another non-invasive technique that detects the electromagnetic fields produced by active neurons. It can identify and provide a precise three-dimensional location of neurons that are synchronously firing, either spontaneously or in response to an external stimulus, in restricted cortical areas (Williamson and Kaufman 1990).

Functional MRI relies on the paramagnetic characteristics of deoxyhemoglobin, measuring its concentration changes in brain tissue, in response to task dependent neuronal activation. The MRI scanner can detect this concentration difference and the computed signal is called blood oxygen-level dependent (BOLD) signal (Rossini et al. 2003). The summation of all the BOLD signals acquired repeatedly over time, permits to detect the task dependent activation with good anatomical resolution within a relatively short period. fMRI measures the blood oxygen level dependent signal. Changes in deoxyhaemoglobin concentration are dependent on blood flow, blood volume, and blood oxygen saturation. When neurons are active, they need more oxygen and glucose so blood flow increases. However, the increase in perfusion overcompensates for the increase in oxygen consumption, thus causing a decrease in local deoxyhaemoglobin concentration (Logothetis et al. 2001). The temporal resolution of fMRI is determined

by the haemodynamic response and can detect differences in peak activation time between brain regions in the order of 1–2 s (Menon and Kim 1999). Together PET and fMRI give a comprehensive view of the distributed network that governs a particular brain function and provide a detailed analysis of the relation between function and anatomy. However, both techniques have several limitations: the sequence of activation events can be too quick to be accurately recorded; the inability to differentiate excitation from inhibition; and lack of discrimination between motor output and sensory feedback (Frostig et al. 1990).

Temporal resolution in fMRI, on the other hand, if compared to the rapidity of neuronal activity is limited by the timing of the hemodynamic response (neurovascular coupling). Both PET and fMRI pose problems in discriminating the temporal sequence of a phenomenon and in differentiating neuronal firing decrease from increase (exciting vs inhibiting net effects).

TMS is increasingly utilized to study brain plasticity. TMS, through a brief and intense magnetic field, is applied directly to the scalp, and it permits, by recording the evoked responses, to map the cortical representation areas located under the coil (Siebner et al. 2000)

TMS and MEG allow the detection of sensorimotor area reshaping, either due to neuronal reorganization or to recovery of the previously damaged neural network. They have a high temporal resolution but suffer from limitations. TMS, in fact, only provides bi-dimensional scalp maps while MEG allows for three-dimensional identification of sources obtained by means of inverse procedures that rely on the choice of a mathematical model of the head and sources. Nonetheless, a multi-technological combined approach in which functional MRI and PET, despite their poor temporal resolution, are integrated with TMS and MEG, constitute at present, the best way to evaluate plasticity phenomena underlying partial or total recovery of hand function.

Another promising computational EEG approach is the analysis of the EEG rhythms (theta, alpha, and beta) generated in different cortical areas as task activation related changes (Houdayer et al. 2006).

*It is probably only through the integration of different neuroimaging techniques that it will be possible to overcome the pitfalls of each methodology, in the study of both normal brain function as well as post-stroke recovery (Rossini et al. 2003).*

## **2.2 ACTIVITIES STUDIED WITH THE COMPLEXITY OF DISTINGUISHING STUDY 1 and STUDY 2**

The purpose of this research was to contribute to the understanding of the neural consequences of the applied therapeutic FES to promote reaching and grasping. The idea was to understand the mechanism



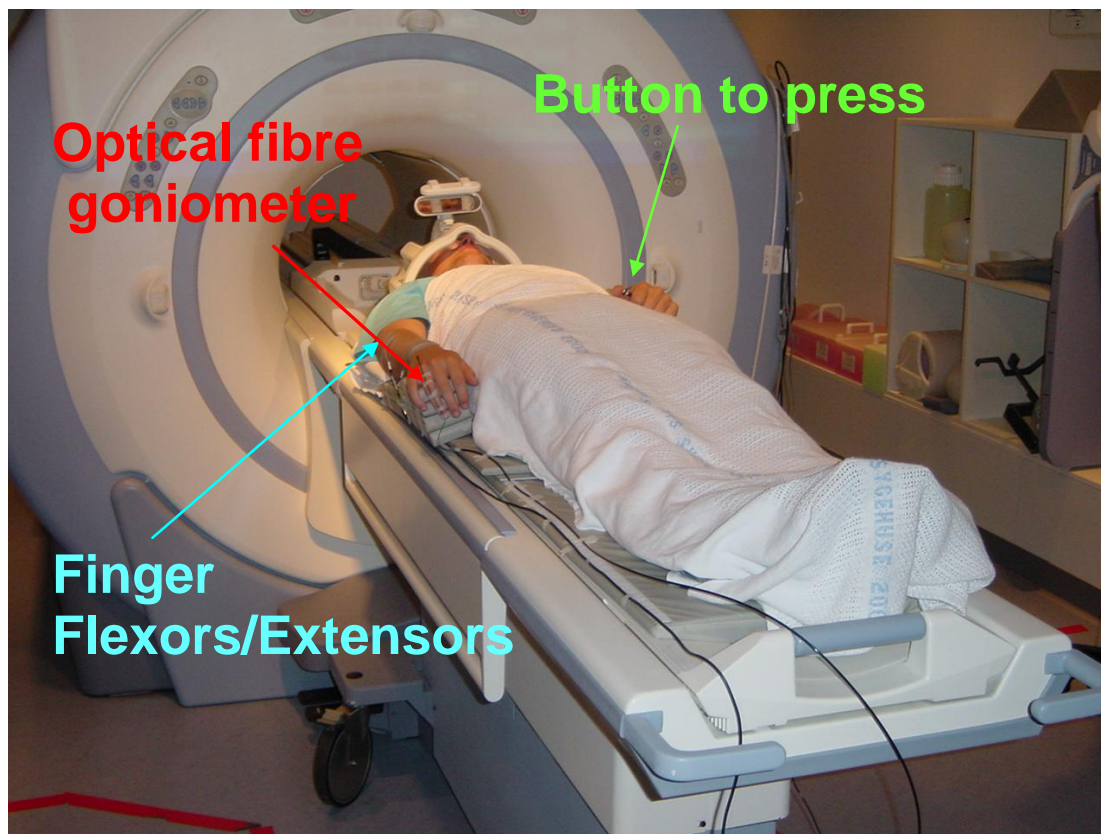
behind therapeutic FES used in clinical rehabilitation. Patterned electrical stimulation was applied on the right arm and the cortical activity elicited by neuromuscular stimulation combined with voluntary effort was assessed, for details see (DOI 10.1002/hbm.21191). Studies 1 and Study 2 were comparing directly and in a controlled setting, the interactions between brain activities generated by voluntary movement, electrically evoked movement and imagined movement. Study 1 used as technique fMRI (see Figure 1) while Study 2 used EEG (see Figure 2).

Temporal resolution of fMRI is bound by the time constants of neurovascular coupling and it cannot describe the dynamics of mental activity at the millisecond level. The EEG is capable of detecting changes in electrical activity in the brain on a millisecond-level making it as one of the few techniques available that has such high temporal resolution.

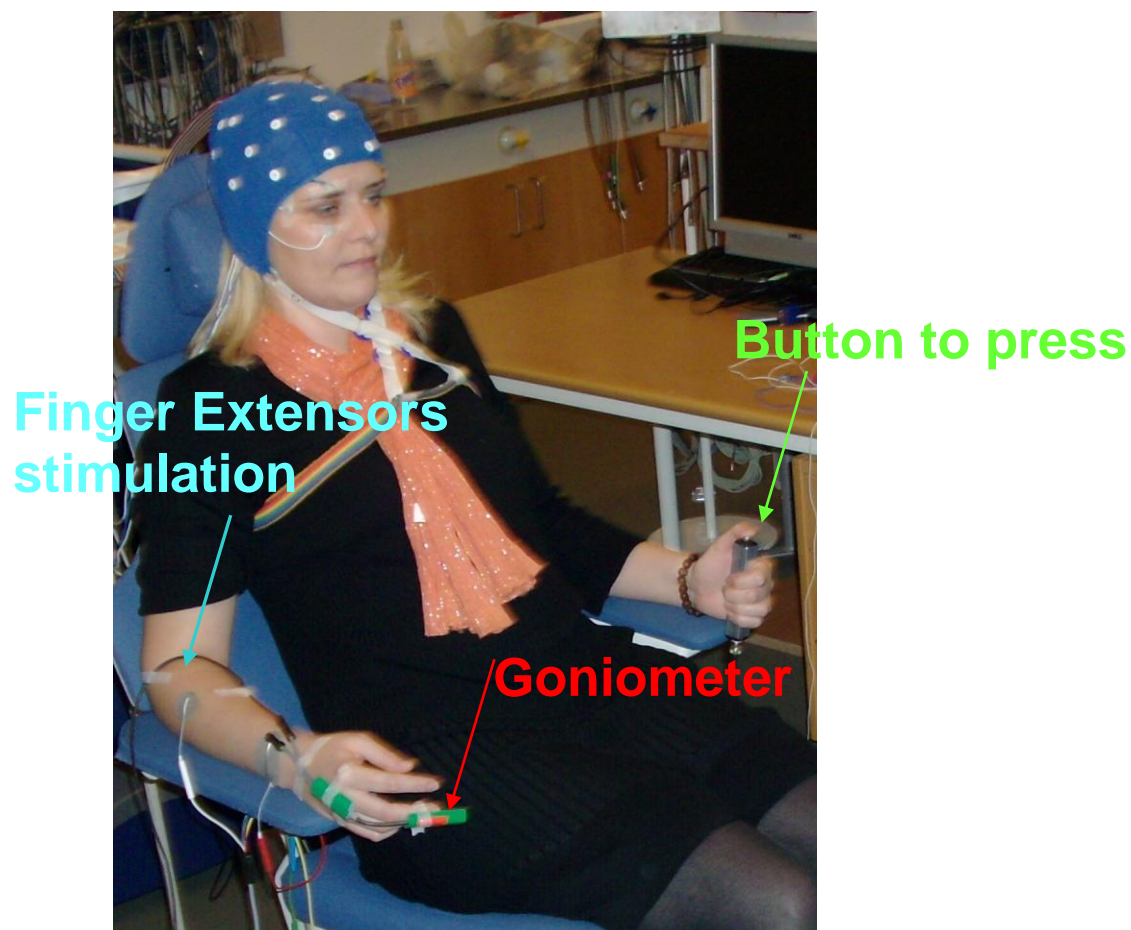
fMRI allows an anatomically detailed measurement of neuronal activity including that of deeper cerebral structures. However, for EEG, attempts to localize the neural sources of the surface electric field are compromised by the “inverse problem”: a given electromagnetic field registered by scalp EEG can result from an infinite number of different intracranial sources. Therefore, the topographical analysis of surface EEG is limited in terms of its localizing capabilities. EEG is relatively tolerant of subject movement versus an fMRI (where the subject must remain completely still). EEG is silent, which allows for better study of the responses to auditory stimuli and does not cause claustrophobia. Hardware costs are significantly lower for EEG sensors versus an fMRI machine. EEG can be used in subjects who are incapable of making a motor response. Evoked response potentials (ERPs) can elucidate stages of processing (rather than just the final end result). More details are presented in Table 1.

	<b>fMRI</b>	<b>EEG</b>
<b>Ability to measure both cortical and deep structures</b>	yes	no
<b>Spatial resolution</b>	1 mm	cm
<b>Temporal resolution</b>	s	ms
<b>Invasiveness of method</b>	no	no
<b>Injection of radioactive isotopes</b>	no	no
<b>Tolerance of technique to subjects movements</b>	no	yes
<b>Silence</b>	Ear plugs	yes
<b>Claustrophobia</b>	Could be	no
<b>Costs</b>	high	low
<b>Phase of movement</b>	final	Evoked responses potentials (ERP): different stages (plan, prepare and execute)
<b>Electrodes on scalp</b>	no	yes (which may bother some people)

**Table 1 Strong points for fMRI and EEG techniques**



**Figure 1** Experimental setup for Study 1. The subjects lay supine on the scanner bed with their arms resting comfortably by their side for the duration of the experiment. An optic fibre goniometer monitored the extent of finger flexion/extension. Electrical stimuli were delivered through round surface stimulation electrodes that were fixed to the skin. The stimulation pattern was triggered by a push-button switch held in the left hand.

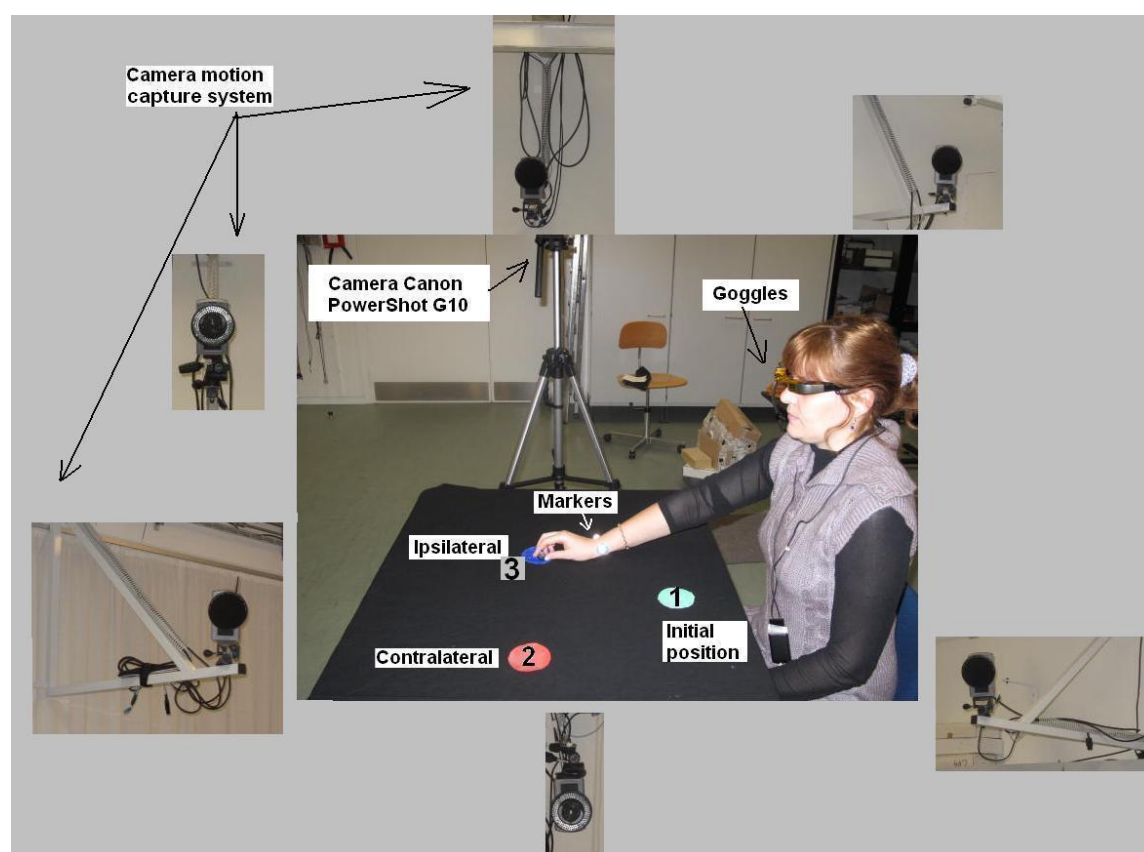


**Figure 2** Experimental setup for Study 2. The subjects lay on an armchair. A goniometer monitored the extent of finger flexion/extension. Stimulation was delivered through round surface stimulation electrodes that were fixed to the skin. The electrodes were positioned with cathodes over the motor points of the extensors (*extensor digitorum communis*) and a common anode located on the forearm near the wrist. The stimulation pattern was triggered by a push-button switch held in the left hand. The EEG recordings were performed with 32 channel digital DC EEG amplifier.

## 2.3 STUDYING LEARNING

### STUDY 3

The necessity for learning comes after stroke due to the fact that proprioception/exteroception is modified and motor pathways do not operate; however the vision works fine. Study 3 is presenting how the learning takes place when vision is modified, while the proprioception/exteroception and motor pathways are intact (see Figure 3). The modified visual input was created using special glasses that presented the view as recorded by a video camera placed at various positions around the subject. The camera was positioned at a frontal (F), lateral (L), or top (T) position with respect to the subject. We studied the differences between the hand trajectories while grasping between altered vision and normal vision (N). The outcome measures from the analysis were the trajectory errors and the time of execution. A detailed description of the experimental setup and the results are included in (DOI pii: 520781).



**Figure 3.** Experimental setup for Study 3. The workspace placed on the desk in front of the subject consisted of 3 colored spots: initial hand position (spot 1, green), contralateral target (spot 2, red) and ipsilateral target (spot 3, blue). We used an optoelectronic motion capture system (ProReflex MCU240, Qualisys, SE) with six cameras positioned around the workspace. Two reflective markers ( $\varnothing$  12 mm) were placed on the wrist of the subject at the

ulnar and radial styloid processes, respectively. The subject viewed the workspace through goggles (Myvu Crystal Standard/Universal) connected to a camera (Canon PowerShot G10). The Canon camera was placed in 3 different positions with respect to the workspace, resulting in 3 different experimental conditions: frontal (F), lateral (L, shown in this figure), and top (T).

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## CHAPTER 6

### DISCUSSIONS

This research seeks to determine the neural consequences of the applied therapeutic FES to promote reaching and grasping. In parallel with the neural consequences of the therapeutic FES, the role of the modified vision in reaching and grasping was determined.

The potential benefits to be gained by this research will be the objective understanding of the effective therapeutic FES treatment that assist post stroke individuals in achieving the hand/arm/leg function, as well as other vital functions, and to return to independent life-style in the easiest, simplest, and fastest way. This information will be extremely beneficial for the researchers investigating optimal methods of intervention for stroke survivors. In addition, in Study 3 we presented an effective, yet simple new tool for altering visual input when studying motor coordination. The results show that this alteration of the visual input can be graded; hence, allow studying of different concepts of learning of the movement. The methodology introduced here may be further explored for various experimental paradigms.

The results of this PhD thesis should be understood as contribution to the rehabilitation field. The studies tried to use the available technology to answer the questions raised by the open identified problems.

#### **6. 1 STUDY 1**

The main research question was: what is the most appropriate technique to quantify the neural consequences of the therapy? This main question leads us to the following specific research questions: is fMRI an appropriate objective technique to evaluate the neural consequences of the therapeutic FES? A summary is included below.

The internal model concept is important in rehabilitation because the model can be updated as the state of the limb changes. To determine if internal models are appropriately incorporated during FES-assisted voluntarily movement, one must test if internal model networks are appropriately engaged during the task. We designed an fMRI experiment to study brain activity evoked with three tasks hand grasp tasks involving voluntary motor activation (VOL), patterned electrical stimulation of finger flexor/extensor muscles to effect movement without voluntary activation (FES), and voluntary activation performed together with FES (FESVOL). Based on the studies of (Blakemore et al. 1998b; Blakemore et al. 1999; Blakemore et al. 2001), which specifically test mechanisms of the internal model networks, we hypothesized that FESVOL, as opposed to FES would activate the motor part of the cerebellum (Grodd et al. 2001), in particular to make predictions of the sensory consequences of motor commands. In turn, this



should reduce the SII activity in FESVOL compared with FES due to a better prediction of the sensory input.

FESVOL revealed greater cerebellar activity compared with FES alone and reduced activity bilaterally in secondary somatosensory areas (SII) compared with VOL alone. Reduced activity was also observed for FESVOL compared with FES alone in the angular gyrus, middle frontal gyrus and inferior frontal gyrus. These findings indicate that during the VOL condition the cerebellum predicts the sensory consequences of the movement and diminish the subsequent activation in SII. The decreased SII activity may reflect a better match between the internal model and the actual sensory feedback. The greater cerebellar activity coupled with reduced angular gyrus activity in FESVOL compared with FES may indicate that the cortex may interpret sensory information during the FES condition as an error-like signal due to the lack of a voluntary component in the movement.

### **6.1.1 MAIN RESULTS STUDY 1:**

- ✓ The greater cerebellar activity coupled with reduced angular gyrus activity in FESVOL compared with FES may indicate that the cortex may interpret sensory information during the FES condition as an error-like signal due to the lack of a voluntary component in the movement.
- ✓ The combination of voluntary activity with FES- driven motor activity may help to make the movement more predictable and, ultimately, more one's own.
- ✓ An alternative explanation for the FESVOL finding is that the voluntary effort reduces the SII activation and increases the cerebellar activation, and on top of this activation the electrical stimulation activates the SII but not the cerebellum. This condition would then look more like the VOL condition, which is likely better integrated than the FES alone condition. In part, this might explain the common notion among FES practitioners why therapeutic FES appears to produce better clinical results than does FES training alone.

### **6.1.2 IMPLICATIONS OF THE RESULTS FOR REHABILITATION**

Our findings have implications for the physical rehabilitation of stroke related deficits. By combining patterned electrical stimulation with attempts at voluntary movement, the movement might become one's own and like ordinary voluntary movement will co-activate the motor control regions and the sensory-feedback areas, and this co-activation may be crucial in motor recovery at the brain level. This may partly explain why therapeutic FES (i.e. FES augmented voluntary activity) produces better clinical results than does FES training alone.

One limitation of our results is that the findings in healthy brains cannot be not directly translated to patient populations. These findings might be completely different from what ones would observe in damaged brains. Patients with brain damage have obviously a neural re-organization and plasticity that is not observed in healthy subjects.

## **6. 2 STUDY 2**

The main research question was: what is the most appropriate technique to quantify the neural consequences of the therapy? This main question leads us to the following specific research questions: is EEG an appropriate objective technique to evaluate the neural consequences of the therapeutic FES? Could EEG analysis complement our previous fMRI results helping through a better understanding of the mechanism by which therapeutic FES interacts with the central nervous system which may allow us to improve the therapy? More specifically: will different task-related afferent input be reflected in the modulation of alpha and beta rhythms and movement related cortical potentials?. A summary is included below. Our study demonstrates that different task-related afferent inputs were reflected in the modulation of alpha and beta rhythms. In addition, the three tasks VOL, FES, and FESVOL utilized a different distribution of brain areas for the preparation, execution and control phases of the movement as quantified by MRCPs. The EEG analysis is complementing our previous fMRI results helping through a better understanding of the mechanism by which therapeutic FES interacts with the central nervous system which may allow us to improve the therapy. Future studies should investigate whether patients with altered strengths of afferent input show similar patterns.

### **6.2.1 MAIN RESULTS STUDY 2:**

- ✓ VOL, FES, FESVOL determine different distribution in brain areas in preparation and execution phases of the movement as quantified by movement-related cortical potentials (MRCPs).
- ✓ The three different task-related afferent inputs were reflected in the modulation of alpha and beta rhythms.

### **6.2.2 IMPLICATIONS OF THE RESULTS FOR REHABILITATION**

MRCPs were studied in connection with stroke rehabilitation. Studies demonstrated topographical alterations of some MRP components during the recovery period after a stroke (Honda et al. 1997; Green et al. 1999; Platz et al. 2000). The strength of the EEG technique is its high temporal resolution, which allows the separate assessment of movement preparation and movement execution and makes it possible

to distinguish slowly evolving movement-related potentials and sensorimotor rhythms, and thereby different types of electric brain activity that are closely related to neural function.

Our results indicate that alpha band energy showed a bilateral decreased distribution over the motor areas and ipsilateral parietal (in relation to the right hand involved in the task). Beta showed an ipsilateral centroparietal decrease. EEG combined with fMRI studies showed that the strength of rolandic alpha, and rolandic beta rhythms inversely correlates with the fMRI signal in ‘its cortical area’. A decrease in the power of sensorimotor rhythms could be correlated to an activated cortical network, servicing planning and execution, while power increase, might reflect deactivation. (Laufs et al. 2003) found robust pattern of negative correlation between BOLD signal change in association with alpha power in frontal and parietal cortices. (Goldman et al. 2002) also observed BOLD signal changes in parts of the frontal and of the occipital lobe to correlate negatively with alpha power. In summary, the bilateral activation might reflect an excitatory activity.

(Platz et al. 2000; Muller et al. 2003) studied movement-related slow cortical potentials and event-related desynchronization of alpha (alpha-ERD) and beta (beta-ERD) activity after self-paced voluntary triangular finger movements in 13 ischaemic supratentorial stroke patients. The multimodal EEG analysis suggested impairment-specific changes in the movement-related electrical activity of the brain. The readiness potential of paretic subjects was centered more anteriorly and laterally; during movement, they showed increased beta-ERD at left lateral frontal recording sites. Patients showed reduced alpha-ERD and beta-ERD during both movement preparation and actual performance. They concluded that (i) disturbed motor efference is associated with an increased need for excitatory drive of pyramidal cells in motor and premotor areas or an attempt to drive movements through projections from these areas to brainstem motor systems during movement preparation; (ii) an undisturbed somatosensory afference might contribute to the release of relevant cortical areas from their ‘idling’ state when movements are prepared and performed; and (iii) patients have a relative lack of activity of the frontal motor system and the left parietal cortex.

## **6.3 STUDY 3**

The main research question was: how the learning takes place when vision is modified, while the proprioception/exteroception and motor pathways are intact? A summary is included below.

### **6.3.1 MAIN RESULTS STUDY 3:**

- ✓ The results indicate that fast learning (recalibration) of the visual systems occurred relatively fast and has been created through the training of movement.

- ✓ The recalibration is more difficult to achieve for altered vision in frontal and lateral conditions than in top condition
- ✓ The paper presents an effective, yet simple new tool for altering visual input when studying motor coordination.
- ✓ The results show that this alteration of the visual input can be graded; hence, allow studying of different concepts of learning of the movement.
- ✓ The methodology introduced here may be further explored for various experimental paradigms, especially if the camera connected to the input of the Myvu Crystal EV is replaced with the computer output providing virtual reality.

Study 3 tested a new tool for studying motor learning/coordination under altered visual input. In the experiment, the visual input was presented to subjects in four different conditions: normal (N), frontal (F), lateral (L), and top (T). The experiment consisted of five sessions that took place on five consecutive days as follows. Day 1 was used for the baseline assessment. Day 2, 3, and 4 were allocated for training. Day 5 was used for evaluation. This paper was intended as a possible application for people after a CVA. The necessity for learning comes after stroke due to the fact that proprioception/exteroception is modified and motor pathways do not operate; however the vision works fine. The goal was to determine how exactly practice makes perfect and how the visual system coordinates with the motor system.

Therefore we looked at the dissociation between proprioception and vision during manipulation of the arm in reach to grasp task. This dissociation translated in additional cognitive operations (translation, rotation, scaling of the visual input on the screen of the goggles into the plane of motion of the arm on the table) that are presumably required to translate visual information about target location on the monitor screen into an estimate of the metrics of the desired arm movement.

Proprioception contrasted with vision, so the brain computing tried a way to recalibrate reference frame for that computation. Errors scaled proportionally with the difficulty of the task. Our subjects ranked the level of difficulty of the F condition as the highest, followed by the L and T conditions.

On Day 1, the errors were generally larger for L condition than for F condition. The largest values for the contralateral 1 EE and ipsilateral EE were observed in the L condition, while the contralateral 2 EE reached a maximum value in the F condition.

This suggests that altered vision in the L condition had the greatest effect on segments 1 and 2, while altered vision in the F condition mostly affected segment 3 of the movement.

Some adaptation occurred even on Day 1 for F and L conditions from the first trials performed. The error decreased from Trial 1 to Trial 10 for F and L conditions through this adaptation was not complete at the end of the 10 trials.

On Day 5, the magnitude of the errors decreased for F and L conditions compared with Day 1. F condition showed the largest decrease of contralateral 2 EE, while L condition for ipsilateral EE (> 50% Day 1). This suggests that the training had the greatest effect on segment 3 for F condition and segment 1 and 2 for L condition.

The magnitude of the errors was substantially smaller in T condition compared with F and L condition both on Day 1 and Day 5.

This trend is consistent with the scatter plot of the trajectory end points (see DOI pii: 52078) and the analysis of velocity profiles (see DOI pii: 520781).

On Day 1, F and L condition, i.e. with the camera positioned in front and lateral (right) to the subject respectively, showed trajectories end points scattered covering almost the entire workspace. T condition, with the camera positioned on top of the subject showed end points clustered together within the reference spots.

The analysis of velocity profiles showed that the adaptation occurred for F, L, T conditions in the way that the velocities had near symmetrical bell-shaped profiles. The peak velocity reached the value typical of normal reaching movements for L condition (segment 1, 3, and 4), for F (segment 2 and 4), for T condition (segment 3), see (DOI pii: 520781).

### **6.3.2 IMPLICATIONS OF THE RESULTS FOR REHABILITATION**

#### *Generalization to other type that was not trained*

The subjects were trained only in F condition. However, the results indicate an improved performance on Day 5 for the L and T conditions, although these conditions were not used for training. It could indicate that training only with F condition affected the motor learning ability of the subjects in general. Learning reach to grasp new trajectories and the new use of the hand in injured persons could be a possible application of the results of this paper.

#### *Cognitive component*

Our results suggest that the difference between altered vision tasks and normal visually guided reaching leads to an adaptation in the form of perceptual recalibration where proprioception was calibrated in terms of the visual system. If the adaptation is expected to take the guise of a more cognitive, problem-solving process, we can refer to this as the visual-motor skill acquisition. The ability to predict with some confidence which of these two types of adaptation a peripheral manipulation will produce would allow for a prediction of whether significant improvement is likely to occur on training, how persistent the adaptation will be, and whether it will result in after-effects. The methodology introduced here may be

further explored for various experimental paradigms; the manipulation of viewing angle would be useful is not reachable working space for disable patients (Ward and Frackowiak 2006).

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## CHAPTER 7

### CONSIDERATIONS AND FUTURE PROSPECTIVES

The present PhD thesis offered an overview of the strong and weak points and contribution of different techniques and methods in defining objectively the neural consequences of the therapeutic FES (STUDY 1 and STUDY 2) and how the learning takes place when vision is modified, while the proprioception/exteroception and motor pathways are intact (STUDY 3).

The participants involved in all three studies were healthy volunteers. The protocol in STUDY 1 and STUDY 2 tried to mimic the clinical therapeutic FES applied to post-stroke patients. It would be of interest to apply the protocol in STUDY 1 and STUDY 2 in patients who had major disability in their paretic hand and arm. However, the extension of the results to the stroke population should be done cautiously. In post stroke patients there is invariably some degree of functional recovery, ranging from minimal to complete.

Functional imaging studies of the motor system in previously hemiparetic patients have described task-related brain activation in recovered patients over and above control subjects in contralesional sensorimotor and premotor cortex, ipsilesional cerebellum, bilateral supplementary motor area (SMA) and parietal cortex (Weiller et al. 1992). (Ward et al. 2003) asked control subjects to perform passive movement of the wrist and obtained increases in brain activation in the contralateral sensorimotor cortex and supplementary motor area, the bilateral inferior parietal cortex and secondary somatosensory areas, and the ipsilateral cerebellum. Increases in brain activation correlating with motor recovery were observed in both the ipsilesional primary sensory and primary motor cortex in 1 patient with good motor recovery but not in another patient with poor recovery. They concluded that functionally relevant changes in cerebral organization can be identified in individual patients.

Healthy volunteer group results are very important for having a ‘proof of principle’. Functional imaging techniques can be used as estimators of the outcome of an applied therapy and can contribute toward an understanding of the general principles of cerebral reorganization after stroke. But we should consider of course the intersubject variability in post stroke population.

In addition, STUDY 1 investigates the short term effect of applied peripheral electrical stimulus combined with voluntary effort. It will be of great interest to investigate the long term effects and to describe the learning process that will occur. Current models of motor learning suggest that during early learning, there is a dynamic interaction between a frontoparietal network encoding movement in terms of spatial coordinates, that requires high levels of attention, and motor cortex which encodes movement in terms of a kinematic system of joints, muscles, limb trajectories, etc. Motor cortex is dominant once learning has occurred and a movement has become automatic (Hikosaka et al. 2002). A number of empirical findings support such a model: decreases in brain activation as a function of motor learning



have been reported in lateral premotor cortex, prefrontal cortex, pre-SMA, superior parietal cortex, anterior cingulate, cerebellum, cerebellar vermis and caudate (Hikosaka et al. 2002); the cerebellum is involved in detecting error between internal models of movement and the sensory consequences of actual movement (Blakemore et al. 1998; Blakemore et al. 2001). (Ward et al. 2003; Ward 2005) describe decreases in activation with recovery consistent with the notion of a transfer of reliance from the frontoparietal to the primary motor system.

### *Technical Challenges and Issues in Experimental Design and Analysis*

The results of functional imaging experiments are only as reliable as the care with which the experiment is constructed and executed. The choice of experimental task, patient monitoring, patient selection, and approaches to analysis require careful consideration if a study is to successfully address its stated hypothesis. Thereafter any functional recovery is associated with a focusing of brain activation patterns towards that seen in controls (Ward 2005). This focusing is similar to that seen in the normal brain during motor skill learning. However, although it is unsurprising that the damaged brain will attempt to use highly preserved neural systems such as those subserving motor skill learning to maximize functional motor recovery, the degree to which this is successful will depend on the integrity of such networks (Ward 2005).

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## SUMMARY

Functional Electrical Stimulation is used in the rehabilitation therapy of patients after stroke to improve their motor abilities. Electrical stimulation when paired with voluntary component (therapeutic FES), appears to facilitate recovery in an additive or interactive way, in clinical studies. An open issue is represented by the mechanisms for these observed effects. Having a good understanding of how therapeutic FES may interact with the central nervous system may therefore be crucial to improve and optimize the treatment. Noninvasive techniques to study brain function, including functional magnetic resonance imaging, electroencephalography, could help to document objectively the relationship between cortical reorganization and the recovery of motor function.

The goal of this thesis was therefore to develop a set of methods and tools that can study plasticity induced by different experimental conditions. The methods that we propose here should be understood as contribution to the actual effort of the researchers in the rehabilitation field.

We started by applying fMRI technique to obtain objective information about the neural consequences of neuromuscular stimulation combined with voluntary effort (FESVOL) peripheral electrical stimulation alone (FES) or voluntary activation alone (VOL) (STUDY 1). The aim was to develop a tool for study plasticity induced by therapeutic FES. The importance of studying the neural correlates associated with FES for clinical populations (ie., stroke) and therapeutic application constituted the motivation for conducting the research. FESVOL revealed greater cerebellar activity compared with FES alone and reduced activity bilaterally in secondary somatosensory areas (SII) compared with VOL alone. Reduced activity was also observed for FESVOL compared with FES alone in the angular gyrus, middle frontal gyrus and inferior frontal gyrus. These findings indicate that during the VOL condition the cerebellum predicts the sensory consequences of the movement and diminish the subsequent activation in SII. The decreased SII activity may reflect a better match between the internal model and the actual sensory feedback. The greater cerebellar activity coupled with reduced angular gyrus activity in FESVOL compared with FES may indicate that the cortex may interpret sensory information during the FES condition as an error-like signal due to the lack of a voluntary component in the movement.

Functional MRI relies on the paramagnetic characteristics of deoxyhemoglobin, measuring its concentration changes in brain tissue, in response to task dependent neuronal activation. fMRI pose problems in differentiating neuronal firing decrease from increase (exciting vs inhibiting net effects). The polarity and amplitude of the potentials observed in the electroencephalogram are directly related to modality (excitatory or inhibitory) and intensity of the neural population at the cortical level. A more complete picture of the cortical reorganization and when and where changes take place could be obtained

with multimodal approaches. The presented limitations lead us to the Study 2 where we applied EEG technique to obtain objective information about the neural consequences of the therapeutic FES.

STUDY 2 evaluated the relationship between different task-related afferent inputs and cortical function. Cortical function was assessed with analysis of the strength of alpha and beta oscillatory activity and movement related cortical potentials in multichannel surface EEG. The working hypothesis was that processing of peripheral electrical stimulus input is reflected differently in the modulation of cortical alpha and beta oscillatory activity and movement related cortical potentials as the procession of the voluntary input.

The first main finding was that different task-related afferent inputs determine different distribution in brain areas in preparation and execution phases of the movement as quantified by movement related cortical potentials. The second main finding was that different task-related afferent inputs are producing a state of activation/deactivation (inhibition) of neural networks in different cortical areas reflected in the modulation of alpha and beta rhythms.

Plasticity of the cortex is considered as learning of novel tasks. The necessity for learning comes after stroke due to the fact that proprioception/exteroception is modified and motor pathways do not operate; however the vision works fine. STUDY 3 tested a novel tool for studying motor coordination with an altered visual input. The altered visual input was created using special glasses that presented the view as recorded by a video camera placed at various positions around the subject. The camera was positioned at a frontal (F), lateral (L), or top (T) position with respect to the subject. We studied the differences between the hand trajectories while grasping between altered vision and normal vision (N) in ten subjects. The outcome measures from the analysis were the trajectory errors and the time of execution. We found substantial trajectory errors and an increased execution time at the beginning of the task. We also found that the trajectory errors decreased after three days of practice with the altered vision for 20 minutes per day, suggesting that recalibration of the visual systems occurred relatively quickly. The results indicate that this recalibration has occurred by movement training. The results also suggest that the recalibration is more difficult to achieve for altered vision in F and L conditions than in T condition.

The potential benefits to be gained by this research will be the objective understanding of the effective therapeutic FES treatment that assist post stroke individuals in achieving the hand/arm/leg function, as well as other vital functions, and to return to independent life-style in the easiest, simplest, and fastest way. This information will be extremely beneficial for the researchers investigating optimal methods of intervention for stroke survivors. In addition, in STUDY 3 we presented an effective, yet simple new tool for altering visual input when studying motor coordination. The results show that this alteration of the visual input can be graded; hence, allow studying of different concepts of learning of the movement. The methodology introduced here may be further explored for various experimental paradigms.

The results of this PhD thesis should be understood as contribution of the available technology to the rehabilitation field. The present PhD thesis offered an overview of the strong and weak points and contribution of different techniques and methods in defining objectively the neural consequences of the therapeutic FES (STUDY 1 and STUDY 2) and the role of normal/modified vision for the control of reaching, grasping, manipulating movement of the arm that can be implemented in neural prosthesis for grasping or artificial hands (STUDY 3).

## SAMMENFATNING

Funktionel Elektrisk Stimulation anvendes ved genoptræning af patienter efter et slagtilfælde, for at forbedre deres motoriske færdigheder. Elektrisk stimulation parret med en voluntær bevægelse (terapeutisk FES) synes, i kliniske studier, at lette genoptræning på en additiv eller interaktiv facon.

Hvilke mekanismer der ligger til grund for de observerede effekter, er et åbent spørgsmål. En god forståelse af hvordan terapeutisk FES kan interagere med det centrale nervesystem, kan derfor være afgørende for at forbedre og optimere behandlingen. Ikke-invasive metoder til at undersøge hjerneaktivitet, som Funktionel magnetisk resonans-billeddannelse og Elektroencefalografi, kan på en objektiv måde dokumentere sammenhængen mellem kortikal reorganisation og genoptræning af motoriske færdigheder.

Målet med afhandlingen var derfor at udvikle metoder og værktøjer, der kunne undersøge plasticitet under forskellige eksperimentielle forhold. De metoder vi foreslår skal forstås som et bidrag til den aktuelle forskning indenfor genoptræning.

Vi startede med at anvende fMRI teknik for, på en objektiv måde, at få information om de neurale konsekvenser af dels neuromuskulær stimulation kombineret med en voluntær bevægelse (FESVOL), periferisk elektronisk stimulation (FES) og voluntær bevægelse (VOL) (STUDIE 1). Målet var at udvikle et værktøj til at undersøge plasticitet som følge af terapeutisk FES. Vigtigheden af at undersøge de neurale korrelater associeret med FES ved kliniske populationer (dvs. slagtilfælde) og terapeutiske anvendelser, udgjorde motivationen for at udføre forskningen. FESVOL viste større cerebellar aktivitet sammenholdt med FES og mindre aktivitet bilateralt i sekundære somatosensoriske områder (SII) sammenholdt med VOL. Reduceret aktivitet blev også observeret for FESVOL sammenholdt med FES i den angular gyrus, den middle frontal gyrus og den inferior frontal gyrus. Disse resultater indikerer, under VOL, at cerebellum prædikterer de sensoriske konsekvenser af bevægelsen og reducerer den efterfølgende aktivering i SII. Den reducerede SII aktivitet kan afspejle et bedre match mellem den interne model og det aktuelle sensoriske feedback. Den større cerebellar aktivitet og reduceret angular gyrus aktivitet i FESVOL sammenholdt med FES kan indikere, at cortex fortolker sensorisk information i løbet af FES som et fejllignende signal, grundet mangel på en voluntær komponent i bevægelsen.

Funktionel MRI er afhængig af de paramagnetiske karakteristika af deoxyhemoglobin ved måling af ændringer i dets koncentration i hjernevæv, som reaktion på opgaveafhængig neuronal aktivering. Det er problematisk for fMRI at skelne en forøgelse i neuronal affyring fra en formindskelse (dvs. ophidsende kontra hæmmende effekt). Polariteten og amplituden af de observerede potentialer i det elektroencefalografi er direkte relateret til modalitet (excitatoriske eller hæmmende) og intensitet af den neurale population, på det kortikale plan. Et mere fuldstændigt billede af den kortikale reorganisation, og

hvornår og hvor ændringer finder sted, kunne opnås med multimodale metoder. De præsenterede begrænsninger førte os til STUDIE 2 hvor vi anvendte EEG teknikker for objektivt at opnå information om de neurale konsekvenser af terapeutisk FES.

STUDIE 2 evaluerede sammenhængen mellem forskellige opgave relaterede afferente input og kortikal funktion. Kortikal funktion blev vurderet ud fra en analyse af styrken af alpha og beta oscillerende aktivitet og bevægelses relateret kortikal potentialer i multikanal overflade EEG. Hypotesen var, at behandling af perifere elektriske stimulus input, reflekteres forskelligt i modulationen af kortikal alpha og beta oscillerende aktivitet, og bevægelses relateret kortikal potentialer.

Det første hovedresultat var, at forskellige opgave relaterede afferente input bestemmer forskellige fordelinger i områder i hjernen, i forbindelse med forberedelses og udførelses faser af bevægelsen, kvantificeret ved bevægelses relateret kortikal potentialer. Det andet hovedresultat var, at forskellige opgave relaterede afferente input, producerer en tilstand af aktivering/deaktivering af neurale netværk i forskellige kortikal områder, der er afspejlet i modulationen af alpha og beta rytmerne.

Plasticitet af cortex betragtes som læring af nye opgaver. Behovet for at lære efter et slagtilfælde skyldes, at proprioception/exteroception er ændret og motor veje ikke virker; dog fungerer synet fint. Studie 3 testede et nyt værktøj til at undersøge motor koordination med et ændret visuelt input. Det ændrede visuelle input blev skabt ved at benytte specielle briller, der viste et billede optaget af et kamera, som blev placeret forskellige steder rundt om forsøgspersonen. Kameraet blev opstillet i en frontal (F), lateral (L) og top (T) positioner i forhold til forsøgspersonen. For ti forsøgspersoner, med normalt og ændret syn, undersøgte vi forskelle i deres hånds bane ved opsamling af et emne. De opsamlede målinger fra analysen var afvigelser fra banen og udførelsestid. Vi fandt betydelige afvigelser fra banen og en forøget udførelsestid i begyndelsen af opgaven. Vi observerede også, at afvigelser fra banen aftog efter tre dages træning, 20 minutter pr. dag., med ændret syn, hvilket antyder, at rekalkibrering af det visuelle system sker relativt hurtigt. Resultatet indekterer, at denne rekalkibrering skyldes bevægelses træning. Resultaterne indikerer også, at rekalkibrering er sværere at opnå for ændret syn (F) og (L) end (T).

De potentielle fordele der kan opnås med denne forskning, vil være den objektive forståelse af effektiviteten af terapeutisk FES behandling, der hjælper post slagtilfælde personer i at opnå brug af hånd/arm/ben og andre vitale funktioner, og til at vende tilbage til en uafhængig livsstil på den letteste, simpleste og hurtigste måde. Denne information vil være yderst gavnlig for forskere, der undersøger optimale metoder til intervention for overlevende der er blevet ramt af et slagtilfælde. Derudover præsenterede vi i STUDIE 3 et effektivt og simpelt nyt værktøj til ændring af visuelt input ved undersøgelse af motor koordinering. Resultaterne viser, at ændring af visuelt input kan gradueres, og det er dermed muligt at undersøge forskellige aspekter ved indlæring af bevægelse. Den introducerede metode kan undersøges yderligere gennem forskellige eksperimentelle paradigmer.

Resultaterne af denne ph.d. afhandling skal ses som et bidrag til den tilgængelige teknologi inden for genoptræning. I denne ph.d afhandling gives et overblik over de stærke og svage sider af forskellige teknikker og metoder, der objektivt definerer de neurale konsekvenser af terapeutisk FES (STUDIE 1 og STUDIE 2), og betydningen af normalt/ændret syn i forbindelse med styring af en arms række og gribe bevægelser, generelt manipulation af en arms bevægelser, der kan implementeres i en neural protese til at gribe med, eller i kunstige hænder (STUDIE 3).